REMARKS

Applicant thanks Examiner Nguyen for pointing out three errors in the response, dated January 26, 2004. Applicant submits this new response and amendment, which applicant believes is fully responsive to the Examiner's August 27th Office Action. Applicant has corrected the errors identified by the Examiner and notes that no amendments were intended in claims 1, 5, and 13; they are indeed presented in the response in their previously presented forms. In addition, applicant has reviewed the other pending claims for additional typographical errors and corrected a misspelling in claims 15 and 23. No other errors were found. The Examiner is invited to contact applicant's representative if additional errors are located.

Receipt of the non-final Office Action mailed August 27, 2003 is acknowledged. Applicant notes that the Examiner and applicant agree that the Office Action is non-final and applicant requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Applicant wishes to draw the Examiner's attention to a typographical error on the cover page of the specification filed on October 19, 1999. The cover page states "Application for U.S. Letters Patent, Entitled: MINIMAL PROMOTERS AND USES THEREOF claiming priority to provisional application serial no. 60/104,781, filed October 19, 1999." The filing date of the provisional application serial no. 60/104,781 was, in fact, October 19, 1998. Please note that the first paragraph on page 1 of the specification properly references the provisional application with the correct filing date. The cover page in the specification has therefore been amended.

A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

Claim 21 has been rewritten in independent form. This amendment is not a narrowing amendment related to patentability; rather, it is intended to be, and should be considered as, an amendment that maintains the scope of claim 21, but places it in independent form.

Claim 24 has been cancelled.

Claims 28-41 have been added. Support for new claims 29-30, 32-34, 36-37, and 39-41 can be found in original claims 16, 17, 20, 21, and 22. Support for new claims 28, 31, 35, and 38 can be found at page 13, ll. 7-27 and page 14, ll. 8-16.

After amendment, claims 1-23, 25, and 28-41 are pending in this application. Claims 9, 10, 18, and 19 are withdrawn from consideration and claims 24, 26, and 27 have been cancelled, leaving claims 1-8, 11-17, 20-23, 25, and 28-41 for consideration by the Office.

There are seven rejections of record and one objection of record. First, claims 1-8, 11-12, 15-17, 20, and 23-25 stand rejected under 35 USC § 112, ¶ 1 as allegedly being unpatentable for containing subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the invention was filed, had possession of the claimed invention. Second, claims 1-8, 11-17, 20, 23, and 25 stand rejected under 35 USC § 112, ¶ 1 as allegedly being unpatentable for failing to enable the full scope of the claims. Third, claim 25 stands rejected under 35 USC § 102(b) as allegedly being unpatentable over Hoffman et al., Proc. Natl. Acad. Sci. 93:5185-90, 1996 ("Hoffman"). Fourth, claims 24 and 25 stand rejected under 35 USC § 102(e) as allegedly being unpatentable over Gu et al., United States Patent No. 6,200,751 ("Gu"). Fifth, claims 24 and 25 stand rejected under 35 USC § 102(b) as allegedly being unpatentable over Deb et al., J. Virology 66:6164-70, 1992 ("Deb"). Sixth, claims 1-3, 5-8, 12-13, and 24-25 stand rejected under 35 USC § 102(e) as allegedly being unpatentable over Bujard et al., United States Patent No. 5,888,981 ("Bujard"). Finally, claims 24 and 25 stand rejected under 35 USC § 102(e) as allegedly being unpatentable over Chao et al., United States Patent No. 6,369,825 ("Chao"). Claims 21 and 22 are objected to as being dependent upon a rejected base claim, but the Examiner acknowledges that these claims would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Applicant respectfully traverses these rejections and objections. Applicant notes with appreciation that the Office has withdrawn all other rejections.

I. The Specification Adequately Describes Minimal Promoters

Claims 1-8, 11-12, 15-17, 20, and 23-25 stand rejected under 35 USC § 112, ¶ 1 as being unpatentable for allegedly containing subject matter which is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the invention was filed, had possession of the claimed invention. This is a new rejection that was not necessitated by the amendment to claims 1 and 25 nor by the submission of an IDS.

Without acquiescing in the rejection and without intending to abandon claimed subject matter but solely to expedite allowance, claim 24 has been cancelled. Thus, applicant respectfully submits that the rejection is moot with respect to claim 24.

As to the merits of the other claims, the Examiner states that the instant specification discloses the preparation of three minimal promoters (human cytomegalovirus ("hCMV"), simian cytomegalovirus ("sCMV"), and pseudorabies virus promoters ("PRV") represented by SalI/BamI, SalI/ScaI, and SalI/NotI fragments of their respective enhanced promoters. But, the Examiner contends that the instant specification fails to provide a representative number of species for a broad genus of minimal promoter that has the same or similar functional properties as those described, e.g., to express the coding sequence of an antigen in an amount sufficient to elicit an immune response to the antigen, particularly a dramatically increased antibody production relative to the enhanced promoters *in vivo*.

The written description requirement ensures that, as of the filing date, the inventor conveyed with reasonable clarity to those of skill in the art that he was in possession of the subject matter of the claims. The written description requirement does not compel the applicant to describe exactly the subject matter claimed, instead the description must clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed. Applicant respectfully submits that he satisfied these requirements and has adequately described all of the claimed elements.

First, applicant notes that he is only required to describe the invention as it is claimed. Applicant submits that the Examiner improperly requires the applicant to describe features that

do not form a part of the claim, such as features that result in "a dramatically increased antibody production relative to the enhanced promoters *in vivo*." *See* Office Action. Claim 1, on the other hand, recites a "minimal promoter sequence operably linked to a coding sequence for the antigen, whereafter said antigen is expressed in said mammalian cells in an amount sufficient to elicit an immune response to the antigen." This sequence, therefore, is what must be described by the applicant in the specification. As will be discussed below, applicant submits that he fully described what is claimed.

A promoter is well known in the art as a segment of a nucleic acid sequence to which a polymerase attaches, thereby aligning the polymerase so that transcription will initiate at a specific site in an operatively connected site. As a result, the minimal promoters described operably link to coding sequences for an antigen and initiate expression of the antigen in mammalian cells. Applicant respectfully submits that he has consistently and sufficiently described such minimal promoters as those promoters where the native enhancer sequence is excluded. Specifically, the specification states:

> A minimal promoter is used in the present invention. The minimal promoter sequence is generally derived from a DNA virus. Typically, the promoter is a promoter which is associated with an early viral gene and usually modulated by an upstream or downstream enhancer element. The promoter sequence is used in its enhancerless form (i.e., it is not couple with its native enhancer sequence when used in the context of the present invention, however, it may be used in a construct which contains other heterologous enhancer sequences).

See page 10, ll. 7-13. In addition, applicant has described where the minimal promoter sequence is generally derived and how it can be isolated or produced. *See* page 10, ll. 7-10 and page 15, ll. 9-28 ("Both the sequence for the minimal promoter and the coding sequence of interest can be obtained and/or prepared using known methods. . . . Furthermore, the desired gene or promoter sequence can be isolated directly from cells and tissues containing the same, using standard techniques, such as phenol extraction and PCR of cDNA or genomic DNA."). Applicant further described several specific examples of minimal promoters. *See* page 10 of the specification, ll. 17-26 and page 24, ll. 8-14. It is well settled that patent applicants are not required to disclose

every species encompassed by their claims, even in an unpredictable art. *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991) (*quoting In re Angstadt,* 537 F.2d 498, 502-03 (CCPA 1976)). Such disclosure would be overwhelming for both applicants and examiners. Accordingly, applicant respectfully submits that the description of the minimal promoters, in combination with the specific examples of minimal promoters, is sufficient to clearly allow persons of ordinary skill in the art to recognize that the applicant invented what is claim.

II. The Specification Enables One of Ordinary Skill in the Art to Make and Use Minimal Promoters

Claims 1-8, 11-17, 20, 23, and 25 stand rejected under 35 USC § 112, ¶ 1 as allegedly being unpatentable for failing to enable the full scope of the claims. The Examiner acknowledges that the specification is enabling for a method of obtaining expression of an antigen of interest in a mammalian subject, which method comprises transferring into cells of said subject a nucleic acid construct comprising a minimal promoter sequence operably linked to a coding sequence for the antigen, whereafter said antigen is expressed in said mammalian cells in an amount sufficient to elicit an immune response to the antigen, and wherein the minimal promoter sequence consists essentially of a hCMV immediate early promoter sequence, a sCMV immediate early promoter sequence, a PRV early promoter region, or a functional variant thereof. Moreover, the Examiner acknowledges that particles coated with the nucleic acid construct described above and suitable for use in particle-mediated nucleic acid immunization are enabled as is a particle acceleration device loaded with the same coated particles. However, the Examiner states that the specification does not enable compositions containing a nucleic acid construct comprising any minimal promoter sequence; a method of using these composition; and a vaccine composition containing these nucleic acid constructs.

The Examiner asserts that the claims are broadly related to any minimal promoter and that the state of the art at the time of the filing was unpredictable because genetic vaccine technology was just emerging and because strong viral promoters were being used at the time. Moreover, the Examiner argues that it is difficult to predict from studies in mice whether the same

constructs would work in humans. Applicant respectfully submits that he has enabled one of skill in the art to practice the invention commensurate in scope with the claims.

It is well settled that the applicant must provide a specification that enables a person reasonably skilled in the art to make and use the claimed invention without undue experimentation. The fact that some experimentation may be employed, however, does not make it undue if a person of skill in the art typically engages in such experimentation. This is because the prohibition is against "undue experimentation," not merely "experimentation." *In re Angstadt,* 537 F.2d 498, 502-03 (CCPA 1976). Requiring the applicants to provide an exhaustive experimental study into any and all possible embodiments would discourage disclosure of discoveries and is in direct contradiction of the principles underlying 35 U.S.C. § 112. *See, e.g., Rohm & Haas Co. v. Dawson Chemical Co.*, 217 USPQ 515, 563-64 (S.D. Tex. 1983), *rev'd on other grounds*, 220 USPQ 289 (Fed. Cir. 1983), cert. denied, 469 U.S. 851 (1984).

Applicant respectfully submits that one of skill in the art would not have to perform undue experimentation to form the nucleic acid construct containing a minimal promoter as claimed and to transfer the construct into the cells of a subject to determine if the antigen is expressed in the mammalian cells in an amount sufficient to elicit an immune response to the antigen. Moreover, applicant submits that he provided sufficient guidance on how to make and use the claimed invention. Each step in this sequence is described so that one of skill in the art would know how to make and use the elements necessary to carry out claims 1-8, 11-17, 20, 23, and 25.

The specification enables one of ordinary skill in the art to make a minimal promoter. Specifically, the specification states:

> A minimal promoter is used in the present invention. The minimal promoter sequence is generally derived from a DNA virus. Typically, the promoter is a promoter which is associated with an early viral gene and usually modulated by an upstream or downstream enhancer element. The promoter sequence is used in its enhancerless form (i.e., it is not couple with its native enhancer sequence when used in the context of the present invention, however, it

> may be used in a construct which contains other heterologous enhancer sequences).

See page 10, ll. 7-13. Applicant has described where minimal promoter sequences are generally derived and how they can be isolated or produced. *See* page 10 of the specification, ll. 7-10. The specification has described which portion of the full promoter must be removed or excluded in order to create a minimal promoter. *See* page 10 of the specification, ll. 10-13.

Moreover, the specification has described how to make the nucleic acid construct. Particularly, it states:

> Both the sequence for the minimal promoter and the coding sequence of interest can be obtained and/or prepared using known methods. . . . Furthermore, the desired gene or promoter sequence can be isolated directly from cells and tissues containing the same, using standard techniques, such as phenol extraction and PCR of cDNA or genomic DNA.

See page 15, ll. 9-17. Applicant further described several specific examples of minimal promoters. *See* page 10, ll. 17-26 and page 24, ll. 8-14. Applicant submits that this disclosure is sufficient to support a broad genus directed to any minimal promoter.

The specification suggests that one of skill in the art would know how to make and use minimal promoters as claimed and that one of skill in the art would know how to make and use the nucleic acid constructs as claimed. Along these lines, applicant submits that since the Examiner does not assert that claim 24 (now cancelled), which was drawn to a purified, isolated minimal promoter sequence, is not enabled, then the other claims relating to a minimal promoter should not be rejected for lack of enablement. Further, the specification describes how to determine whether an amount of antigen of interest sufficient to mount an immunological response and how such amount can be readily determined by one of skill in the art. *See* page 18, ll. 18-25. Finally, the specification fully describes the vaccine composition of claim 25 and how to make it. *See* page 18, ll. 18 through page 21, ll. 10 and Examples 1 and 2. If one of ordinary skill in the art carries out these described steps, he or she can, without undue experimentation, make and use the claimed invention commensurate with the scope of the claims. Accordingly, applicant respectfully requests that this rejection be reconsidered and withdrawn.

III. Claims 1-3, 5-8, 12-13, and 24-25 are Not Anticipated by the Prior Art of Record

A determination that a patent is invalid as being anticipated under 35 U.S.C. § 102 requires a finding that "each and every limitation is found either expressly or inherently in a single prior at reference." *Celeritas Techs. Inc. v. Rockwell Int'l Corp.* , 150 F.3d 1354, 1360 (Fed. Cir. 1998).

The Hoffman Article

Claim 25 stands rejected under 35 USC § 102(b) as allegedly being unpatentable over Hoffman. Claim 25 recites a vaccine composition comprising a nucleic acid construct comprising a coding sequence for an antigen of interest operably linked to a minimal promoter sequence. The Examiner asserts that Hoffman discloses a recombinant retroviral construct containing an autoregulatory cassette comprising a heptamerized tet operator sequence fused to the hCMV immediate early minimal promoter, operably linked to lacZ which encodes a beta-galactosidase. The Examiner argues that Hoffman discloses every limitation of the nucleic acid construct in the vaccine composition of the presently claimed composition. Applicant respectfully disagrees.

Hoffman fails to disclose or teach a vaccine composition comprising a minimal promoter sequence. A minimal promoter sequence as used in the context of the present invention is a promoter that excludes the native enhancer sequence of that promoter. *See* page 10 of the specification, ll. 7-13. Hoffman does not disclose, explicitly or inherently, the exclusion or removal of the native enhancer sequence from the promoter it discusses, hCMV. Rather, Hoffman discloses exchanging the 3' LTR of pBABE M lacZ with the mutant 3' LTR of pJrPro-, which lacks the promoter and enhancer sequences in the 3' LTR. *See* Hoffman, page 5186, Vector Construction. Hoffman does not, however, suggest that the native enhancer is removed from the relatively weak $P_{hCMV*-1}$ promoter that is used in the article. To the contrary, Hoffman suggests that the potential interference of the viral enhancer and promoter with the $P_{hCMV*-1}$ promoter is eliminated by the use of the mutant 3' LTR of pJrPro- in the SIN vector, which lacks the viral enhancer and promoter. *See* Hoffman, page 5187, left column. As a result, Hoffman

fails to disclose or teach a vaccine composition comprising a minimal promoter sequence and therefore reconsideration and withdrawal of this rejection is requested.

Moreover, Hoffman's use of the term "minimal promoter" in the article is an inconsistent usage of the term used in the present claims. While the applicant discloses and claims an actual promoter sequence devoid of native enhancer sequences, Hoffman is using the term to refer to the relatively weak $P_{hCMV*-1}$ promoter, which is not devoid of its native enhancer sequence.

The Gu Patent

Claims 24 and 25 stand rejected under 35 USC § 102(e) as allegedly being unpatentable over Gu. Claim 24 recites an isolated, purified minimal promoter sequence. Claim 25 recites a vaccine composition comprising a nucleic acid construct comprising a coding sequence for an antigen of interest operably linked to a minimal promoter sequence. The Examiner asserts that Gu discloses the isolation and uses of the minimal promoter of the endothelial cell protein C binding protein, EPCR, operably linked to a gene coding for a protein of interest in expression vectors, including plasmid vectors. The Examiner further contends that the promoter disclosed in Gu, including a region resulting in selective expression in endothelial cells, between –1 and –220, based on the positions relative to the ATG encoding the first amino acid of the murine EPCR protein, meets the limitation of the "minimal promoter" of the instant invention. Applicant respectfully traverses this rejection.

Without acquiescing in the rejection and without intending to abandon claimed subject matter but solely to expedite allowance, claim 24 has been cancelled. Thus, applicant respectfully submits that the rejection is moot with respect to claim 24.

Gu fails to disclose or teach a vaccine composition comprising a minimal promoter sequence. A minimal promoter sequence as used in the context of the present invention is a promoter that excludes the native enhancer sequence of that promoter. *See* page 10 of the specification, ll. 7-13. Gu does not disclose, explicitly or inherently, the exclusion or removal of the native enhancer sequence from the promoter, nor does it enable such a promoter. In fact, all of the permutations disclosed in Gu include the full promoter sequence –1 to –220. Gu merely

discloses the removal of a control element responsive to thrombin, referred to as "B," and the removal of a repressor sequence, referred to as "C." As a result, Gu fails to disclose or teach a vaccine composition comprising a minimal promoter sequence and therefore reconsideration and withdrawal of this rejection is requested.

Moreover, Gu's use of the term "minimal promoter" in the article is an inconsistent usage of the term used in the present claims. While the applicant discloses and claims an actual promoter sequence devoid of native enhancer sequences, Gu is referring to a section within one of two natively enhanced promoter sequences. Applicant respectfully requests that this rejection be withdrawn.

The Deb Article

Claims 24 and 25 stand rejected under 35 USC § 102(b) as allegedly being unpatentable over Deb. Claim 24 recites an isolated, purified minimal promoter sequence. Claim 25 recites a vaccine composition comprising a nucleic acid construct comprising a coding sequence for an antigen of interest operably linked to a minimal promoter sequence. The Examiner asserts that Deb discloses a plasmid comprising a minimal human proliferating cell antigen (PCNA) promoter with a TATA box alone operably linked to a CAT gene for transfection in Hela cells. The Examiner further asserts that a bacterial chloramphenicol acetyltransferase gene product is an antigen since it is capable of eliciting an immunological response in a host. Applicant respectfully traverses this rejection.

For the reasons set forth above, the rejection is moot with respect to claim 24.

Deb fails to disclose or teach a vaccine composition comprising a minimal promoter sequence. A minimal promoter sequence as used in the context of the present invention is a promoter that excludes the native enhancer sequence of that promoter. *See* page 10 of the specification, ll. 7-13. Deb discloses the use of the TATA sequence. A TATA box, as disclosed in Deb, is an adenine- and thymine-rich promoter sequence located 25-30 base pairs upstream of a gene, which is the binding site of RNA polymerase. This disclosure does not constitute, either explicitly or inherently, a disclosure of the exclusion or removal of the native enhancer sequence

from a promoter, nor does it enable such a promoter. Moreover, the Examiner does not identify a teaching in the reference of a minimal promoter, i.e., a promoter where the native enhancer sequence is excluded.

The Bujard Patent

Claims 1-3, 5-8, 12-13, and 24-25 stand rejected under 35 USC § 102(e) as allegedly being unpatentable over Bujard. The Examiner asserts that that Bujard discloses both in vivo and ex vivo methods for a regulated expression of a gene of interest in a cell in a subject, including a human, using a tetracycline controlled expression system. The Examiner further asserts that the regulated expression system comprises a polynucleotide molecule encoding a protein of interest, wherein the polynucleotide is operably linked to a tTA-responsive promoter that contains a minimal hCMV promoter. The Examiner also asserts that Bujard teaches the preparation of two minimal promoters, hCMV-1* and hCMV*-2. Applicant respectfully traverses this rejection.

For the reasons set forth above, the rejection is moot with respect to claim 24.

Bujard fails to disclose or teach a minimal promoter sequence that initiates expression of the antigen in mammalian cells in an amount effective to elicit an immune response to the antigen. The minimal promoters according to the present invention operably link to coding sequences for an antigen and initiate expression of the antigen in mammalian cells. Moreover, applicant respectfully submits that he has consistently and sufficiently described such minimal promoters as those promoters where the native enhancer sequence is excluded. The minimal promoters disclosed in Bujard are unable to activate transcription. *See* Bujard, col. 8, ll. 36-41 (A minimal promoter is a "partial promoter sequence which defines the transcription start site but which by itself is not capable, if at all, of initiating transcription efficiently.") & col. 39, ll. 42-45. As such, Bujard does not disclose or suggest the method set forth in claim 1. Since, claims 2-3, 5-8, and 12-13 depend from claim 1, for at least this reason these claims are patentable over Bujard. Moreover, Bujard fails to disclose or teach a vaccine composition comprising a minimal promoter sequence. Thus, Bujard does not disclose or suggest the vaccine set forth in

claim 25. Applicant therefore respectfully requests that this rejection be reconsidered and withdrawn.

The Chao Patent

Claims 24 and 25 stand rejected under 35 USC § 102(e) as allegedly being unpatentable over Chao. Claim 24 recites an isolated, purified minimal promoter sequence. Claim 25 recites a vaccine composition comprising a nucleic acid construct comprising a coding sequence for an antigen of interest operably linked to a minimal promoter sequence. The Examiner asserts that Chao discloses the preparation of a CMV minimal promoter sequence ID NO:1 to drive the expression of an RNA or a protein in a baculovirus vector and that this vector meets every limitation of the vaccine composition. Applicant respectfully traverses this rejection.

For the reasons set forth above, the rejection is moot with respect to claim 24.

Chao fails to disclose or teach vaccine composition comprising a minimal promoter sequence. The minimal promoters according to the present invention operably link to coding sequences for an antigen and initiate expression of the antigen in mammalian cells. Moreover, applicant respectfully submits that he has consistently and sufficiently described such minimal promoters as those promoters where the native enhancer sequence is excluded. Chao discloses promoters that have all or a portion of SEQ ID:2 removed from the full promoter resulting in SEQ ID:1. Chao does not disclose promoters where the native enhancer sequence is excluded. Thus, not all of the limitations are present in Chao and applicant respectfully requests that this rejection be reconsidered and withdrawn.

IV. Claims 21 -22 and 29-32 are Allowable

Finally, claims 21 and 22 are objected to as being dependent upon a rejected base claim, but the Examiner acknowledges that these claims would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Without acquiescing in the objection and without intending to abandon claimed subject matter but to expedite allowance, claim 21 has been rewritten in independent form to include the limitations of

the base claim. Claim 22 now depends from independent claim 21, which the Examiner has indicated is allowable. Applicant has added dependent claims 29-32, which also depend on claim 21. These claims are similar to original claims 16, 17, and 20. Applicant respectfully requests that these claims be entered and favorably considered.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. § 1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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